FURTHER OBSERVATIONS ON THE EFFECT OF QUININ IN RABIES *

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In a previous paper[1] were given the results of an experiment in which dogs were inoculated with street virus and subsequently given large doses of quinin by mouth. Three dogs, so treated, lived, while the untreated controls died of rabies. The results were summarized as follows: "The above cases are not taken to mean that a cure for developed rabies has been found. It is known that in rabies, as in other diseases, there are variations in severity and virulence in different cases. It is possible that these cases were of sufficiently moderate severity that the quinin furnished barely sufficient aid to enable the system to throw off the disease, and that the same result would not have followed in severe cases. Viewed conservatively, the results are encouraging and indicate that the medical treatment of developed hydrophobia should not be regarded as hopeless. Should quinin not prove efficient when put to more severe tests, other agents should be given thorough trial experimentally."

Absence from laboratory facilities interrupted the further trial of quinin for several months. On resuming the tests, a strain of street virus was selected which was of somewhat greater virulence than that previously used. Street virus was used rather than fixed virus for the reason that it is the type responsible for practically all human cases of hydrophobia, and it was with a view to possible clinical application that the experiments were made. The technic of inoculation was the same as that previously used, i. e., anesthetized dogs were inoculated through the optic foramen by means of a long needle. Rabbits and guinea-pigs were inoculated intracranially through an opening made in the skull by a trocar. At varying periods following the inoculation, quinin was given in large doses either by mouth or by injection. In every case, an inoculated animal was kept untreated as a control. Quinin bisulphate was given by mouth, and, in a few instances, by injection. Otherwise, for both subcutaneous and intravenous admin-

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1. Jour. Infect. Dis., 1913, 13, p. 165.

istrations, the double hydrochlorid of quinin and urea was used. A brief summary of the experiments follows.

GROUP 1

October 31.—Rabbits 1 and 2 were inoculated.

November 15.—Rabbit 1, untreated, died. Negri bodies found in large numbers.

November 11.—Daily subcutaneous injections of 1 c.c. of a 10 percent solution of quinin bisulphate were begun on Rabbit 2. Dense areas of fibrosis and sloughs developed at the sites of injection.

November 21.—Immediate death was caused by 0.5 c.c. of the 10 percent solution, given intravenously. The rabbit had shown no signs of rabies, but Negri bodies were found in smear preparations from the hippocampus.

GROUP 2

November 5.—Rabbits 1 and 2 were inoculated.

November 20.—Rabbit 1, untreated, died. Negri bodies found.

November 9.—Daily subcutaneous injections of 1.5 c.c. of a 10 percent solution of quinin and urea begun on Rabbit 2. Indurations developed at the site of injections.

November 22.—An intravenous injection of 1 c.c. of the 10 percent solution of quinin and urea caused immediate death. The rabbit had shown no signs of rabies, and no Negri bodies were found.

GROUP 3

November 9.—Dogs 1, 2, and 3 inoculated.

November 24.—Dog 1 untreated, died. Negri bodies found. Rabies.

November 11.—Dogs 2 and 3 began receiving daily doses of 0.325 gm. quinin bisulphate by mouth.

November 26.—Dog 2 died. No symptom of rabies. Thick mucopurulent discharge from nose. Lungs consolidated in extensive areas. No Negri bodies found in hippocampus. Gram-positive diplococcus isolated from blood cultures. Guinea-pig, inoculated with substance of hippocampus, lived. Diagnosis, distemper.

December 4.—Dog 3 died with symptoms similar to those of Dog 2. The findings were also similar. Guinea-pig, inoculated with substance of hippocampus, lived. Diagnosis, distemper.

GROUP 4

December 8.—Dogs 1, 2, 3, and 4 inoculated.

January 8.—Dog 1, untreated, died. Combined symptoms of distemper and rabies. Negri bodies numerous. Gram-positive diplococcus cultivated from the blood. Guinea-pig, inoculated with brain, died of rabies. Diagnosis, rabies with distemper.

January 12.—Dog 2, treated since December 15 with quinin, 0.65 gm. daily, died after severe typical course of distemper. Distemper organism cultivated from blood and from bronchial exudate in consolidated lungs. No Negri bodies found. Rabbit, inoculated with brain substance, lived. Distemper. Dogs 3 and 4 died within two weeks following the inoculation. Distemper.

GROUP 5

January 9.—Dogs 1, 2, and 3 inoculated.

January 20.—Dog 1 died of meningitis on the tenth day after inoculation. No Negri bodies found.

January 24.—Dog 2, untreated, died after typical course of rabies. Negri bodies found.

January 28.—Dog 3 died after typical course of rabies. Had received 0.65 gm. of quinin daily since January 17. Negri bodies found. Rabbit, inoculated with brain, died of rabies.

GROUP 6

February 28.—Rabbits 1, 2, and 3 inoculated.

March 7.—Rabbit 1 given daily subcutaneous injections of 0.25 gm. quinin and urea.

March 11.—Indurations developed at site of injections. Given intravenous injection of 0.17 gm. daily.

March 21.—Died. Negri bodies found.

March 10.—Daily intravenous injections of 0.17 gm. begun on Rabbit 2.

March 15.—Died. Negri bodies found.

March 10.—Rabbit 3, untreated control, died. Negri bodies found.

GROUP 7

May 23.—Dogs 1, 2, and 3 were inoculated. Dogs 2 and 3 received 0.65 gm. quinin bisulphate by mouth daily beginning May 25.

June 22.—Dog 1, untreated, died. Negri bodies found in large numbers.

June 29.—Dog 2 died after a characteristic course of rabies. Negri bodies found.

June 15.—Dog 3 became very excitable, restless, and nervous and remained so for two weeks after which he gradually became normal.

June 25.—Guinea-pigs, inoculated intracranially June 18 with saliva of Dog 3, died of meningitis.

June 25.—Guinea-pigs, inoculated intramuscularly with saliva of Dog 3, lived.

QUININ IN HUMAN CASES OF HYDROPHOBIA

Harris[2] reported the successful treatment of a case clinically diagnosed as hydrophobia. The patient, who had been bitten several weeks before, presented symptoms which were sufficiently characteristic to warrant a clinical diagnosis of early hydrophobia. He recovered after intravenous administration of quinin and urea. Wesson[3] and Williams[4] each reports a case of hydrophobia in which quinin was given without success or apparent benefit.

I have had opportunity to treat two developed cases with quinin. The first case was a boy 5 years of age. On January 1, 1914, he was bitten on the face by a stray dog with which he and other children were playing. The dog was not captured and no suspicion of hydrophobia was aroused. On January 29 active symptoms developed, but the disease was not recognized until February 1, 9 a. m. At 3 p. m. when I first saw the boy, he was extremely restless, was able to swallow only with great difficulty, and showed classical hydrophobia and aerophobia. He was able to take 15 gr. quinin bisulphate in three doses by mouth after which he became unable to swallow and quinin and urea were given in

2. Jour. Amer. Med. Assn., 1913, 61, p. 1511.
3. Ibid., 1914, 62, p. 204.
4. Pub. Health Rep., 1914, 29, p. 949.

small doses intravenously and subcutaneously. Fifteen grains were given in the next six hours. The disease, meantime, was progressing rapidly and no effect from the quinin was evident. At 10 p. m., the child developed a severe acute mania on which sedatives had little effect. At 2:30 a. m., he gradually sank into a coma, and died at 12 m., February 2.

Case 2 was a colored woman, aged 60, who was bitten on the hand June 14. On July 24 she became sick, and, on July 27, the disease was recognized and she was brought to the hospital. The symptoms were not marked, and consisted of dizziness, slight difficulty in swallowing, restlessness, well-marked aerophobia, and spasmodic contractions of the muscles of respiration. She was given 20 gr. quinin bisulphate by mouth every two hours from 4 p. m., July 27, until 10 a. m., July 28, after which she became unable to swallow. In the afternoon two intravenous injections of 10 gr. each were given. No delay in the progress of the symptoms was noticed. At 5 p. m., she developed convulsions and acute mania, making restraint necessary. This condition progressed steadily during the night. Death occurred at 7 a. m., July 29.

These cases illustrate the difficulty of applying any measures in the early stages of developed hydrophobia. The disease is not recognized when its symptoms first appear, and when recognized the termination is usually near at hand.

DISCUSSION

In Group 1, the treated rabbit lived six days longer than the control, and died as a result of too large an intravenous injection of quinin. However, Negri bodies were found in the brain which indicates that the treatment had not prevented the disease from developing.

Group 2 was similar in results to Group 1, except that no Negri bodies were found in the brain of the treated rabbit. In both of these groups, the subcutaneous injection of quinin produced dense indurations and necrosis which caused the discontinuation of further treatment by this method. The danger of death, following intravenous injections of quinin in rabbits, and the difficulty of administering quinin by mouth led me to use dogs in the following groups.

In Groups 3, 4, and 6, clear-cut results were prevented by the prevalence for months of a severe form of distemper in the kennels. Repeated disinfections were ineffective in preventing the recurrence of the malady in successive groups. These groups are inconclusive as to the curative effect of quinin, but they are of sufficient significance to warrant their consideration here.

In Group 3, Dogs 2 and 3, quinin treated, died two days and ten days, respectively, later than their untreated controls.

In Group 4, the quinin treated dog died four days later than the control.

In Group 5, one dog, untreated, died on the tenth day from infection of meninges probably introduced at the time of inoculation. The remaining two dogs of the group did not have distemper. The treated dog died four days later than the control, and both died of rabies. This represents a clear-cut failure of quinin to cure or to prevent the development of rabies in dogs.

In Group 6, rabbits were again used and the quinin, in the form of double hydrochlorid of quinin and urea, was given intravenously. The treated rabbits died of rabies five and eleven days, respectively, later than the controls. Again, the treatment neither prevented nor cured the disease.

In Group 7, one treated dog died of rabies seven days later than the control. The other treated dog lived, but the evidence is not conclusive whether the inoculation failed to produce the disease, whether this was one of the so-called abortive cases, or whether the treatment had something to do with the result.

Assuming that each of the treated dogs in Groups 3 and 4 had died of rabies, instead of distemper, the fact remains that, in no case, did the treated animal die as early as the control. If any significance is to be attached to this it would point to the possible application of quinin in human cases when, for any reason, the Pasteur treatment is begun late and a prolongation of the incubation period would give time for the completion of the preventive immunization.

Cummings[5] and Frothingham and Halliday[6] report the unsuccessful treatment of rabbits and guinea-pigs by subcutaneous and intravenous injections of quinin.

CONCLUSIONS

Quinin has failed to be regularly effective as a cure or preventive of rabies in animals.

Quinin, given in the latter stages of hydrophobia in two human cases, produced no significant results.

Quinin appears to retard somewhat the development of street rabies if given in large doses during the incubation period. The results indicate that the organism, which causes rabies, is influenced in some degree by quinin. This is significant as showing that the organism is susceptible to therapeutic measures, and gives reason to hope that some drug may be found which will be of value in the treatment of hydrophobia.

5. Jour. Infect. Dis., 1914, 15, p. 209.
6. Jour. Med. Research, 1914, 30, p. 275.